FORM PTO 1390
(REV 5-93) US DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY DOCKET NUMBER
2001-1749A

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)
09/979509
NEW

International Application No.	International Filing Date	Priority Date Claimed
PCT/JP00/03373	May 25, 2000	May 25, 1999

Title of Invention
MAG EXPRESSION PROMOTERS

Applicant(s) For DO/EO/US
Masakazu KAWASAKI; Nobuharu GOTOH; Yoshiharu HAYASHI; and Kazuyuki KAWASAKI

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.

2. [] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.

3. [X] This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).

4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [X] A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. [] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [] is not required, as the application was filed in the United States Receiving Office (RO/US)

6. [X] A translation of the International Application into English (35 U.S.C. §371(c)(2)).

7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3)).
   a. [] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [] have been transmitted by the International Bureau.
   c. [] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.

8. [] A translation of the amendments to the claims under PCT Article 19.

9. [X] An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)). (UNEXECUTED)

10. [] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 14. below concern other document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. [] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. [X] A FIRST preliminary amendment.

    [] A SECOND or SUBSEQUENT preliminary amendment.

14. [X] Other items or information: (a) PCT Request; (b) Forms PCT/IB/301, 304, 308 and 332; (c) International Search Report; and (d) First page of published International Application (WO 00/71119).

JC10 Rec'd PCT/PTO 23 NOV

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) NEW 09/979509	INTERNATIONAL APPLICATION NO. PCT/JP00/03373	ATTORNEY'S DOCKET NO. 2001-1749A

15. [X] The following fees are submitted

	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):		
Neither international preliminary examination fee nor international search fee paid to USPTO and International Search Report not prepared by the EPO or JPO $1040.00		
International Search Report has been prepared by the EPO or JPO ..... $ 890.00		
International preliminary examination fee not paid ot USPTO but international search paid to USPTO ..... $ 740.00		
International preliminary examination fee paid to USPTO but claims did not satisfy provisions of PCT Article 33(1)-(4) ..... $ 690.00		
International preliminary examination fee paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... $ 100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of $130.00 for furnishing the oath or declaration later than [] 20 [] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate		
Total Claims	24 -20 =	4	X $18.00	$72.00	
Independent Claims	12 - 3 =	9	X $84.00	$756.00	
Multiple dependent claim(s) (if applicable)			+ $280.00	$	

TOTAL OF ABOVE CALCULATIONS =	$1718.00	
[] Small Entity Status is hereby asserted. Above fees are reduced by 1/2.	$	
SUBTOTAL =	$1718.00	
Processing fee of $130.00 for furnishing the English translation later than [] 20 [] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +	$	
TOTAL NATIONAL FEE =	$1718.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40 per property +	$	
TOTAL FEES ENCLOSED =	$1718.00	
	Amount to be refunded	$
	Amount to be charged	$

a. [X] A check in the amount of $1718.00 to cover the above fees is enclosed. A duplicate copy of this form is enclosed.

b. [] Please charge my Deposit Account No. 23-0975 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-0975.

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEES FOR THIS PAPER TO DEPOSIT ACCOUNT NO. 23-0975

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

19. CORRESPONDENCE ADDRESS

000513

PATENT TRADEMARK OFFICE

By Michael R. Davis

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November 23, 2001

[CHECK NO. 47633]

[2001_1749A]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Masakazu KAWASAKI et al.	:	**Attn: BOX PCT**
Serial No. NEW	:	**Docket No. 2001-1749A**
Filed November 23, 2001	:	

MAG EXPRESSION PROMOTERS
[Corresponding to PCT/JP00/03373
Filed May 25, 2000]

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents,
Washington, DC 20231

Sir:

Please amend the above-identified application as follows:

IN THE SPECIFICATION

Please amend the specification as follows:

Page 1, after the title of the invention, please insert the following:

This application is a 371 application of PCT/JP00/03373 filed May 25, 2000.

Please replace the paragraph beginning at page 1, line 29, to page 2, line 11, with the following rewritten paragraph:

The main component forming the myelin sheath is myelin and, as a component to stabilize the multilayer structure of the myelin sheath, myelin specific proteins are known. Of these, proteolipid protein and P_0 protein are involved in crosslinking and adhesion between myelin membranes, and myelin basic protein (hereinafter to be referred to as MBP) is present in the cytoplasm of myelin sheath and involved in compaction of the sheath (Morell P. et al., in Basic Neurochemistry, Siegel GJ et al. Eds. Ravan Press, p. 117-143 (1994)). In addition, myelin-

associated glycoprotein (hereinafter sometimes to be referred to as MAG) is involved in adhesion between axon and myelin sheath (Quarles RH, Myelin-associated glycoprotein: functional and clinical aspects, in Neuronal and Glial Proteins: Structure, Function and Clinical Application, Marangos PJ et al. Eds. Academic Press, New York, p. 295 (1988)).

Please replace the paragraph beginning at page 2, line 23, to page 3, line 7, with the following rewritten paragraph:

In Schwann cell, where MAG is excessively expressed in vitro, myelination is promoted (Owens GC et al., J. Cell Biol., 111, p. 1171-1182 (1990)), but in Schwann cell, where expression of MAG is decreased, myelination is suppressed (Owens GC et al., Neuron, 7, p. 565-575 (1991)). In vivo, the number of myelinated nerves of MAG deficient mice decreases and the number of unmyelinated nerve increases, which is considered to be caused by a retardation in the myelin formation (Bartsch S. et al., Brain Res. 762, p. 231-234 (1997)). On the other hand, there is also a report documenting that, despite a morphological abnormality observed in the periaxonal space between axon and myelin sheath, no difference is found in the number of myelinated nerves, thickness of myelin sheath or the diameter of axon, of the normal mice and MAG deficient mice (Li C. et al. Nature, 369, p. 747-750 (1994)). Therefore, many points remain unknown about the relationship between MAG and myelination.

Please replace the paragraph beginning at page 15, line 30, to line 33, with the following rewritten paragraph:

Fig. 1, Fig. 2 and Fig. 3 are microscopic photographs showing the results of Experimental Example 1, wherein Fig. 1 shows the effect of a negative control compound (DMSO) on myelination of axon.

Please replace the paragraph beginning at page 15, line 34, to page 16, line 2, with the following rewritten paragraph:

Fig. 2 is a microscopic photograph showing the effect of a positive control compound (ascorbic acid) on myelination of axon.

Please replace the paragraph beginning at page 16, line 3, to line 6, with the following rewritten paragraph:

Fig. 3 is a microscopic photograph showing the effect of the compound of the present invention (Y-128 to be mentioned later) on myelination of axon.

IN THE CLAIMS

Please cancel claims 19-30 without prejudice or disclaimer to the subject matter therein.

Please amend claim 5 as follows:

5.(Amended) The MAG expression promoter of claim 1, wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

Please add the following new claims:

34. (New) The MAG expression promoter of claim 2, wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

35.(New) The MAG expression promoter of claim 3, wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

36.(New) The MAG expression promoter of claim 4, wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

REMARKS

The specification has been amended to insert a cross reference to the International application.

Inadvertent errors have also been corrected on pages 1-3 and 15-16, such changes being essentially self-explanatory.

Claim 5 has been amended to depend only from claim 1, to avoid the multiple dependent claim fee, as a result of which new claims 34-36 have been added to the application.

Attached hereto is a marked-up version of the changes made to the specification and claim 5 by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

Masakazu KAWASAKI et al.

By _____
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November 23, 2001

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEES FOR THIS PAPER TO DEPOSIT ACCOUNT NO. 23-0975

VERSION WITH MARKINGS TO SHOW CHANGES MADE

5.(Amended) The MAG expression promoter of [any of] claim 1 [to claim 4], wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

Version with Markings to Show Changes Made

SPECIFICATION

MAG EXPRESSION PROMOTERS

Technical Field

This invention relates to MAG expression promoters. Specifically, the present invention relates to MAG expression promoters useful as an agent for the prophylaxis and/or treatment of diseases mainly presenting hypomyelination, and further, dysmyelination or demyelination. More particularly, the present invention relates to MAG expression promoters containing 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, its optically active form or its pharmaceutically acceptable salt as an active ingredient.

Background Art

Vertebrata have developed myelinated nerve to enable high speed processing of large information. The myelin sheath, which is characteristic of the myelinated nerve, is formed upon enveloping of nerve axon by cytoplasmic membrane of oligodendrocyte or Schwann cell, and has a multilayer structure. As a result, the nerve becomes insulated as well as acquires an extremely high impedance and extremely low capacitance. The sodium channels are present in accumulation in the nodes of Ranvier, which is a cut line between a myelin sheath and another myelin sheath, facilitate saltatory conduction of an impulse and enable high speed processing of information (namely, high nerve conduction velocity).

The main component forming the myelin sheath is myelin and, as a component to stabilize the multilayer structure of the myelin sheath, myelin specific proteins are known. Of these, proteolipid protein and P_0 protein are involved in crosslinking and adhesion between myelin ~~sheets~~ membranes, and myelin basic protein (hereinafter to be

referred to as MBP) is present in the cytoplasm of myelin ~~sheets~~ sheath and involved in compaction of the ~~sheets~~ sheath (Morell P. et al., in Basic Neurochemistry, Siegel GJ et al. Eds. Ravan Press, p. 117-143 (1994)). In addition, myelin-associated glycoprotein (hereinafter sometimes to be referred to as MAG) is involved in adhesion between axon and myelin ~~sheets~~ sheath (Quarles RH, Myelin-associated glycoprotein: functional and clinical aspects, in Neuronal and Glial Proteins: Structure, Function and Clinical Application, Marangos PJ et al. Eds. Academic Press, New York, p. 295 (1988)).

The MAG belongs to the immunoglobulin superfamily and the electrophoretic mobility is 100-kDa. When myelination is started, MAG is expressed by the oligodendrocyte in the central nervous system and by Schwann cell in the peripheral nervous system. The proportion of MAG in myelin is only 1% in the central nervous system and 0.1% in the peripheral nervous system. Recently, it has been clarified that MAG plays not only a role as a simple adhesion molecule but is also positively involved in the formation and maintenance of myelin sheath, as mentioned below.

In Schwann cell, where MAG is excessively expressed in vitro, myelination is promoted (Owens GC et al., J. Cell Biol., 111, p. 1171-1182 (1990)), but in Schwann cell, where expression of MAG is decreased, myelination is suppressed (Owens GC et al., Neuron, 7, p. 565-575 (1991)). In vivo, the number of myelinated nerves of MAG deficient mice decreases and the number of unmyelinated nerve increases, which is considered to be caused by a retardation in the myelin formation (Bartsch S. et al., Brain Res. 762, p. 231-234 (1997)). On the other hand, there is also a report documenting that, despite a morphological abnormality observed in

the ~~contact part~~ periaxonal space between axon and myelin ~~sheet~~ sheath, no difference is found in the number of myelinated nerves, thickness of myelin ~~sheet~~ sheath or the diameter of axon, of the normal mice and MAG deficient mice (Li C. et al. Nature, 369, p. 747-750 (1994)). Therefore, many points remain unknown about the relationship between MAG and myelination.

As regards the molecular mechanism of myelination, there is only a report at present that MAG binds with an axon receptor to activate Fyn tyrosine kinase (Umemori H. et al., Nature, 367, p. 572-576 (1994)), and then promotes expression of MBP gene (Umemori H., J. Neurosci., 19, p. 1393-1397 (1999)), which is not sufficient to clear the mechanism.

As the diseases mainly presenting hypomyelination, and further, dysmyelination or demyelination, multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration, Charcot-Marie-Tooth disease and the like are known (Takeshi Yasuda et al., Clinical Test, 40, p. 760-766 (1996)).

These diseases are reported to be treated with interferon, steroid, γ-globulin, plasma exchange or immunosuppressant (Gen Sobue, Brain and Development, 30, p. 115-120 (1998), Hajime Harukawa et al., Nippon Rinsho, 55, p. 187-194 (1997)), but the situation is not entirely satisfactory. Since in patients with multiple sclerosis, disappearance of MAG in the early stages of onset of the disease is observed (Moller JR, Ann. Neurol., 22, p. 469-474 (1987)), a drug that promotes expression of MAG is expected to be effective for the prophylaxis and/or treatment of the onset of

group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, $-COOH$, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is $-CH(OH)-$, $-C(=O)-$ or $-CH_2-$; and

Z is $=CH-$ or $=N-$,

an optically active form thereof or a pharmaceutically acceptable salt thereof and a written matter associated therewith, the written matter stating that the MAG expression promoter can or should be used for promoting expression of MAG.

(32) The commercial package of the above-mentioned (31), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(33) A commercial package comprising a MAG expression promoter comprising 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof and a written matter associated therewith, the written matter stating that the MAG expression promoter can or should be used for promoting expression of MAG.

Brief Description of Drawings

Fig. 1, Fig. 2 and Fig. 3 are microscopic photographs showing the results of Experimental Example 1, wherein Fig. 1 shows the effect of ~~addition of~~ a negative control compound (DMSO) on myelination of axon.

Fig. 2 is a microscopic photograph showing the

effect of ~~addition of~~ a positive control compound (ascorbic acid) on myelination of axon.

Fig. 3 is a microscopic photograph showing the effect of ~~addition of~~ the compound of the present invention (Y-128 to be mentioned later) on myelination of axon.

Fig. 4 shows an image of an X ray film obtained by Experimental Example 2, and MAG expression in the cells cultured with the compound of the present invention, the negative control compound or the positive control compound.

Fig. 5 shows the results of Experimental Example 3, and the time-course changes in the MAG expression in the cells cultured with the compound of the present invention, the negative control compound or the positive control compound.

Embodiment of Invention

The MAG expression promoter of the present invention encompasses any as long as it can promote *in vitro* or *in vivo* expression of MAG at a gene level or a protein level.

The disease caused by hypomyelination is a disease of mammals inclusive of human, including any disease mainly presenting the disease state of hypomyelination, dysmyelination or demyelination.

Moreover, the disease mainly presenting dysmyelination or demyelination means diseases of mammals inclusive of human, and encompasses any disease mainly presenting the disease state of hypomyelination, dysmyelination or demyelination. Examples thereof include multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic

3/ppts.

SPECIFICATION

MAG EXPRESSION PROMOTERS

Technical Field

This invention relates to MAG expression promoters. Specifically, the present invention relates to MAG expression promoters useful as an agent for the prophylaxis and/or treatment of diseases mainly presenting hypomyelination, and further, dysmyelination or demyelination. More particularly, the present invention relates to MAG expression promoters containing 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, its optically active form or its pharmaceutically acceptable salt as an active ingredient.

Background Art

Vertebrata have developed myelinated nerve to enable high speed processing of large information. The myelin sheath, which is characteristic of the myelinated nerve, is formed upon enveloping of nerve axon by cytoplasmic membrane of oligodendrocyte or Schwann cell, and has a multilayer structure. As a result, the nerve becomes insulated as well as acquires an extremely high impedance and extremely low capacitance. The sodium channels are present in accumulation in the nodes of Ranvier, which is a cut line between a myelin sheath and another myelin sheath, facilitate saltatory conduction of an impulse and enable high speed processing of information (namely, high nerve conduction velocity).

The main component forming the myelin sheath is myelin and, as a component to stabilize the multilayer structure of the myelin sheath, myelin specific proteins are known. Of these, proteolipid protein and P_0 protein are involved in crosslinking and adhesion between myelin sheets, and myelin basic protein (hereinafter to be

referred to as MBP) is present in the cytoplasm of myelin sheets and involved in compaction of the sheets (Morell P. et al., in Basic Neurochemistry, Siegel GJ et al. Eds. Ravan Press, p. 117-143 (1994)). In addition, myelin-associated glycoprotein (hereinafter sometimes to be referred to as MAG) is involved in adhesion between axon and myelin sheets (Quarles RH, Myelin-associated glycoprotein: functional and clinical aspects, in Neuronal and Glial Proteins: Structure, Function and Clinical Application, Marangos PJ et al. Eds. Academic Press, New York, p. 295 (1988)).

The MAG belongs to the immunoglobulin superfamily and the electrophoretic mobility is 100-kDa. When myelination is started, MAG is expressed by the oligodendrocyte in the central nervous system and by Schwann cell in the peripheral nervous system. The proportion of MAG in myelin is only 1% in the central nervous system and 0.1% in the peripheral nervous system. Recently, it has been clarified that MAG plays not only a role as a simple adhesion molecule but is also positively involved in the formation and maintenance of myelin sheath, as mentioned below.

In Schwann cell, where MAG is excessively expressed in vitro, myelination is promoted (Owens GC et al., J. Cell Biol., 111, p. 1171-1182 (1990)), but in Schwann cell, where expression of MAG is decreased, myelination is suppressed (Owens GC et al., Neuron, 7, p. 565-575 (1991)). In vivo, the number of myelinated nerves of MAG deficient mice decreases and the number of unmyelinated nerve increases, which is considered to be caused by a retardation in the myelin formation (Bartsch S. et al., Brain Res. 762, p. 231-234 (1997)). On the other hand, there is also a report documenting that, despite a morphological abnormality observed in

the contact part between axon and myelin sheet, no difference is found in the number of myelinated nerves, thickness of myelin sheet or the diameter of axon, of the normal mice and MAG deficient mice (Li C. et al. Nature, 369, p. 747-750 (1994)). Therefore, many points remain unknown about the relationship between MAG and myelination.

As regards the molecular mechanism of myelination, there is only a report at present that MAG binds with an axon receptor to activate Fyn tyrosine kinase (Umemori H. et al., Nature, 367, p. 572-576 (1994)), and then promotes expression of MBP gene (Umemori H., J. Neurosci., 19, p. 1393-1397 (1999)), which is not sufficient to clear the mechanism.

As the diseases mainly presenting hypomyelination, and further, dysmyelination or demyelination, multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration, Charcot-Marie-Tooth disease and the like are known (Takeshi Yasuda et al., Clinical Test, 40, p. 760-766 (1996)).

These diseases are reported to be treated with interferon, steroid, γ-globulin, plasma exchange or immunosuppressant (Gen Sobue, Brain and Development, 30, p. 115-120 (1998), Hajime Harukawa et al., Nippon Rinsho, 55, p. 187-194 (1997)), but the situation is not entirely satisfactory. Since in patients with multiple sclerosis, disappearance of MAG in the early stages of onset of the disease is observed (Moller JR, Ann. Neurol., 22, p. 469-474 (1987)), a drug that promotes expression of MAG is expected to be effective for the prophylaxis and/or treatment of the onset of

the above-mentioned diseases.

In JP-A-60-34952, JP-B-64-7074, JP-B-3-16348, JP-B-4-15781, JP-B-4-15782, JP-B-5-29031, JP-B-5-41143 and JP-B-5-74589, the compound of the formula (I) to be mentioned below is disclosed, which is useful for the prophylaxis and treatment of thrombosis, stroke, myocardial infarction, sudden cardiac death, angina pectoris, hypertension, asthma, nephritis and the like, optically active forms thereof and pharmaceutically acceptable salts thereof having a pharmacological action, such as potent TXA_2 biosynthesis inhibitory action, platelet aggregation inhibitory action and vasodilating action and the like. WO97/24333 discloses that, of these compounds, 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, optically active forms thereof and pharmaceutically acceptable salts thereof are useful agents for the prophylaxis and/or treatment of diabetic complications.

However, it is not described or suggested that a compound of the formula (I) to be mentioned later has an action to promote expression of MAG.

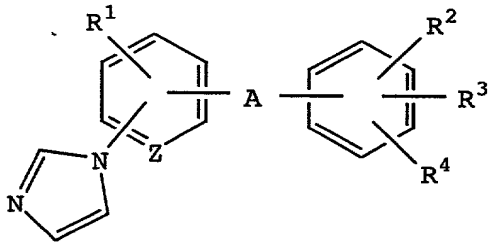
It is an object of the present invention to provide MAG expression promoters. More particularly, an object of the present invention is to provide MAG expression promoters that can be an agent for the prophylaxis and/or treatment of diseases mainly presenting hypomyelination, and further, dysmyelination or demyelination.

Disclosure Of The Invention

The present inventors have conducted intensive studies and found that a compound of the following formula (I), an optically active form thereof and a pharmaceutically acceptable salt thereof promote expression of MAG, and that they are useful as an agent

for the prophylaxis and/or treatment of the diseases mainly presenting hypomyelination, and further, dysmyelination or demyelination, which resulted in the completion of the following invention.

(1) A MAG expression promoter containing a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, $-COOH$, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is $-CH(OH)-$, $-C(=O)-$ or $-CH_2-$; and

Z is $=CH-$ or $=N-$,

an optically active form thereof or a pharmaceutically acceptable salt thereof (hereinafter sometimes to be generally referred to as the compound of the present invention).

(2) The MAG expression promoter of the above-mentioned (1), which is applicable to a disease of mammals inclusive of human, caused by hypomyelination.

(3) The MAG expression promoter of the above-mentioned (1), which is applicable to a disease of mammals

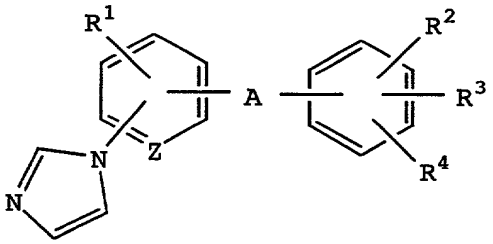
inclusive of human, which disease mainly presents dysmyelination or demyelination.

(4) The MAG expression promoter of the above-mentioned (1), which is applicable to a disease of mammals inclusive of human, which disease being multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration or Charcot-Marie-Tooth disease.

(5) The MAG expression promoter of any of the above-mentioned (1) to (4), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(6) A MAG expression promoter comprising 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof.

(7) A method of promoting expression of MAG, which method comprises administering a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is

a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

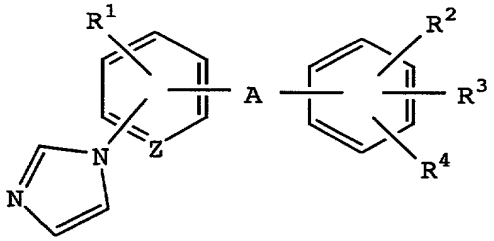
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

(8) The method of the above-mentioned (7), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(9) A method for promoting expression of MAG, which method comprises administering 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

(10) A method for prophylaxis and/or therapy of a disease caused by hypomyelination, which method comprises administering a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with

the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

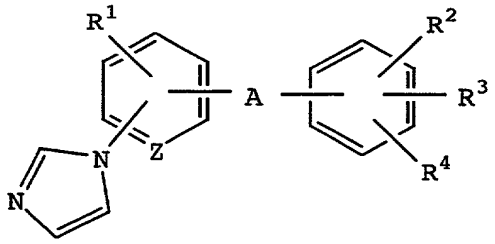
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

(11) The method of the above-mentioned (10), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(12) A method for prophylaxis and/or therapy of a disease caused by hypomyelination, which method comprises administering 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

(13) A method for prophylaxis and/or therapy of a disease mainly presenting dysmyelination or demyelination, which method comprises administering a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with

the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

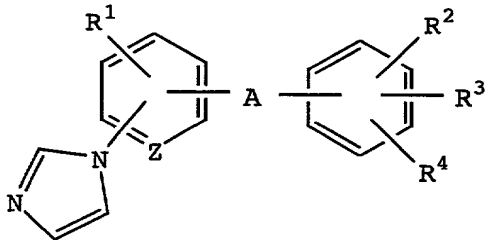
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

(14) The method of the above-mentioned (13), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(15) A method for prophylaxis and/or therapy of a disease mainly presenting dysmyelination or demyelination, which method comprises administering 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

(16) A method for prophylaxis and/or therapy of multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration or Charcot-Marie-Tooth disease, which method comprises administering a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$,

$-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is $-CH(OH)-$, $-C(=O)-$ or $-CH_2-$; and

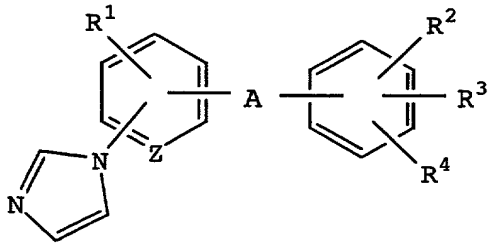
Z is $=CH-$ or $=N-$,

an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

(17) The method of the above-mentioned (16), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(18) A method for prophylaxis and/or therapy of multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration or Charcot-Marie-Tooth disease, which method comprises administering 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

(19) Use of a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;
wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

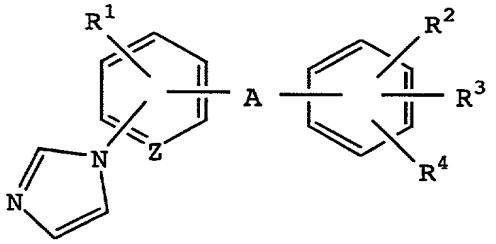
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter.

(20) The use of the above-mentioned (19), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(21) Use of 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter.

(22) Use of a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;
wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is

a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

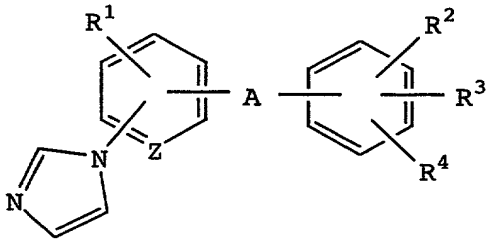
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of human, which is caused by hypomyelination.

(23) The use of the above-mentioned (22), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(24) Use of 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of human, which is caused by hypomyelination.

(25) Use of a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7

in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or -CH_2-; and

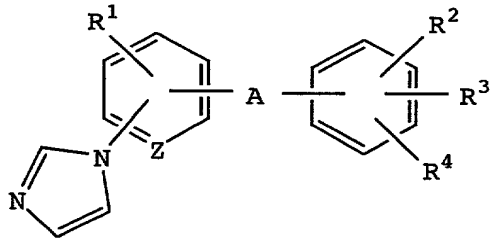
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of human, which mainly presents dysmyelination or demyelination.

(26) The use of the above-mentioned (25), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(27) Use of 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of human, which mainly presents dysmyelination or demyelination.

(28) Use of a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, -$COOR^5$, -$CONR^6R^7$, -$CH_2NR^6R^7$, -CH_2OH or -CH_2OR^8;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7

in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

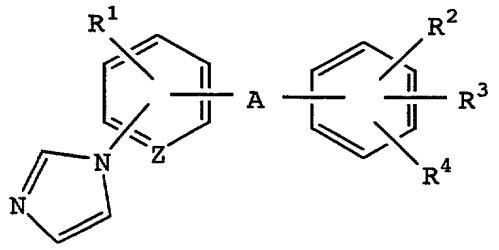
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of human, which is multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration or Charcot-Marie-Tooth disease.

(29) The use of the above-mentioned (28), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(30) Use of 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of human, which is multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration or Charcot-Marie-Tooth disease.

(31) A commercial package comprising a MAG expression promoter comprising a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl

group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, $-COOH$, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is $-CH(OH)-$, $-C(=O)-$ or $-CH_2-$; and

Z is $=CH-$ or $=N-$,

an optically active form thereof or a pharmaceutically acceptable salt thereof and a written matter associated therewith, the written matter stating that the MAG expression promoter can or should be used for promoting expression of MAG.

(32) The commercial package of the above-mentioned (31), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(33) A commercial package comprising a MAG expression promoter comprising 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof and a written matter associated therewith, the written matter stating that the MAG expression promoter can or should be used for promoting expression of MAG.

Brief Description of Drawings

Fig. 1, Fig. 2 and Fig. 3 are microscopic photographs showing the results of Experimental Example 1, wherein Fig. 1 shows the effect of addition of a negative control compound (DMSO) on myelination of axon.

Fig. 2 is a microscopic photograph showing the

effect of addition of a positive control compound (ascorbic acid) on myelination of axon.

Fig. 3 is a microscopic photograph showing the effect of addition of the compound of the present invention (Y-128 to be mentioned later) on myelination of axon.

Fig. 4 shows an image of an X ray film obtained by Experimental Example 2, and MAG expression in the cells cultured with the compound of the present invention, the negative control compound or the positive control compound.

Fig. 5 shows the results of Experimental Example 3, and the time-course changes in the MAG expression in the cells cultured with the compound of the present invention, the negative control compound or the positive control compound.

Embodiment of Invention

The MAG expression promoter of the present invention encompasses any as long as it can promote *in vitro* or *in vivo* expression of MAG at a gene level or a protein level.

The disease caused by hypomyelination is a disease of mammals inclusive of human, including any disease mainly presenting the disease state of hypomyelination, dysmyelination or demyelination.

Moreover, the disease mainly presenting dysmyelination or demyelination means diseases of mammals inclusive of human, and encompasses any disease mainly presenting the disease state of hypomyelination, dysmyelination or demyelination. Examples thereof include multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic

leukodegeneration, Charcot-Marie-Tooth disease and the like.

In the present specification, the definition of each symbol in the formula (I) is as follows.

The halogen atom at R^1 may be chlorine atom, bromine atom, fluorine atom and iodine atom, with preference given to chlorine atom.

The alkyl group at R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 is a linear or branched chain alkyl group having 1 to 10 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl and the like, with preference given to an alkyl group having 1 to 4 carbon atoms.

The alkoxy group at R^1 is linear or branched chain alkoxy group having 1 to 6 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, hexyloxy and the like.

The compound of the present invention can be synthesized according to a method described in JP-A-60-34952, JP-B-64-7074, JP-B-3-16348, JP-B-4-15781, JP-B-4-15782, JP-B-5-29031, JP-B-5-41143 and JP-B-5-74589.

An optically active form of the compound of the present invention can be produced by a conventional method, such as racemic resolution and the like.

A pharmaceutically acceptable salt of the compound of the present invention is exemplified by acid addition salts with inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid and the like, or organic acids, such as fumaric acid, maleic acid, mandelic acid, citric acid, tartaric acid, salicylic acid and the like, salts with a metal such as sodium, potassium, calcium, magnesium, aluminum and the

like, and salts with amino acid such as lysine and the like. In addition, 1/2 hydrate, 1/3 hydrate, 2/3 hydrate, monohydrate, 3/2 hydrate, dihydrate and the like thereof are also encompassed. Salts of these can be produced by a conventional method.

The compound of the present invention can be used as an active ingredient of a MAG expression promoter for promoting the expression of MAG in mammals such as human, cow, horse, dog, mouse, rat and the like. Therefore, the compound of the present invention is useful as an agent for the prophylaxis and/or treatment of diseases mainly presenting hypomyelination, further, dysmyelination or demyelination, particularly as an agent for the prophylaxis and/or treatment of multiple sclerosis, encephalitis, myelitis, Guillain-Barre syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration and Charcot-Marie-Tooth disease.

Of the compounds of the present invention, preferable compounds are as follows.

(1) 2-(1-imidazolyl)-α-(2,4,6-trimethylphenyl)-benzenemethanol

(2) 2-(1-imidazolyl)-2',4',6'-trimethylbenzophenone

(3) 4-(1-imidazolyl)-α-(2,4,6-trimethylphenyl)-benzenemethanol

(4) 3-chloro-4-(1-imidazolyl)-α-(2,4,6-trimethylphenyl)benzenemethanol

(5) 3-(1-imidazolyl)-α-(2,4,6-trimethylphenyl)-benzenemethanol

(6) 2-chloro-5-(1-imidazolyl)-α-(2,4,6-trimethylphenyl)benzenemethanol

(7) 5-(1-imidazolyl)-2-methyl-α-(2,4,6-trimethylphenyl)benzenemethanol and its

monohydrochloride

(8) 5-(1-imidazolyl)-2-methoxy-α-(2,4,6-trimethylphenyl)benzenemethanol

(9) 5-(1-imidazolyl)-2-methyl-α-(4-hydroxymethyl-2,6-dimethylphenyl)benzenemethanol

(10) 2-chloro-5-(1-imidazolyl)-α-(4-hydroxymethyl-2,6-dimethylphenyl)benzenemethanol

(11) 5-(1-imidazolyl)-2-methyl-α-(4-methoxymethyl-2,6-dimethylphenyl)benzenemethanol

(12) 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid and its sodium salt 1/2 hydrate

(13) methyl 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoate

(14) 5-(1-imidazolyl)-2,2',6'-trimethyl-4'-(1-imidazolylmethyl)benzophenone

(15) ethyl 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoate

(16) N-methyl 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzamide

(17) 4-[α-hydroxy-2-chloro-5-(1-imidazolyl)benzyl]-3,5-dimethylbenzoic acid

(18) 4-[α-hydroxy-5-(1-imidazolyl)-2-methoxybenzyl]-3,5-dimethylbenzoic acid

(19) (S)-4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid (hereinafter sometimes to be referred to as Y-128)

(20) 4-[5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid

(21) methyl (S)-4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoate

(22) α-[2-(1-imidazolyl)pyridin-5-yl]-2,4,6-trimethylbenzenemethanol

The MAG expression promoter of the present invention is formulated as a typical pharmaceutical

composition or a pharmaceutical preparation and administered orally or parenterally. For example, the compound of the present invention and a pharmaceutically acceptable carrier (e.g., excipient, binder, disintegrant, corrigent, flavor, emulsifier, diluent, solubilizer etc.) are mixed to give a pharmaceutical composition or a pharmaceutical preparation in a suitable form for oral or parenteral administration. The pharmaceutical preparation includes solid preparation, semi-solid preparation and liquid preparation. Examples thereof include tablet, pill, powder, granule, capsule, troche, syrup, solution, emulsion, suspension, injection (liquid, suspension etc.), suppository, inhalant, percutaneously absorbable drug, eye drop, eye ointment and the like.

When a solid preparation is produced, additives are used. Examples of the additive include sucrose, lactose, cellulose, D-mannitol, maltitol, dextran, starch, agar, arginate, chitin, chitosan, pectin, gum tragacanth, gum arabic, gelatin, collagen, casein, albumin, calcium phosphate, sorbitol, glycine, carboxy methylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, glycerin, polyethylene glycol, sodium hydrogencarbonate, magnesium stearate, talc and the like. Tablets can be prepared into those applied with general coating as necessary, such as sugar-coated tablets, enteric coated tablets and film coated tablets. Moreover, two-layer tablets and multi-layer tablets can be prepared.

When a semi-solid preparation is produced, plant and animal fats and oils (olive oil, corn oil, castor oil etc.), mineral fats and oils (petrolatum, white petrolatum, solid paraffin etc.), waxes (jojoba oil, carnauba wax, bees wax etc.), partially synthesized or

entirely synthesized glycerin fatty acid ester (lauric acid, myristic acid or palmitic acid glyceride etc.) and the like can be used. Examples of commercially available products of these include Witepsol (manufactured by Dynamitnovel Ltd.), Farmazol (NOF Corporation) and the like.

When a liquid preparation is produced, additives are used. For example, sodium chloride, sorbitol, glycerin, olive oil, propylene glycol, ethyl alcohol and the like are used. Particularly, when an injection is produced, a sterile aqueous solution (e.g., physiological saline), an isotonic solution or an oily solution (e.g., sesame oil, soybean oil) is used. Where necessary, a suitable suspending agent (e.g., sodium carboxymethylcellulose), nonionic surfactant, solubilizer (e.g., benzyl benzoate, benzyl alcohol) and the like can be concurrently used. When an eye drop is produced, an aqueous liquid or aqueous solution is used. Particularly, sterile aqueous solution for injection is used. An eye drop may contain various additives, such as buffer, isotonicity agent, solubilizer, preservative, viscosity agent, chelating agent, pH adjusting agent and aromatic as necessary. As the buffer, borate buffer, acetate buffer, carbonate buffer and the like are preferable for reducing stimulation. The pH is preferably adjusted to generally about 6 - 8.5.

The content of the compound of the present invention in a pharmaceutical composition or pharmaceutical preparation is 0.1 - 100 wt% of the pharmaceutical composition or pharmaceutical preparation, which is suitably 1 - 50 wt%. While the dose varies depending on the symptom, body weight, age and the like of patients, it is generally about 0.01 - 100 mg/kg by oral administration for an adult per day,

which is preferably administered once or several times a day. For administration, oral, rectal and parenteral (e.g., muscular, intravenous, percutaneous and subcutaneous) administrations are employed.

Examples

The present invention is explained in detail in the following by referring to Formulation Examples and Experimental Examples. These do not limit the present invention in any way.

Formulation Example 1: film-coated tablet

Y-128	50.0 mg
D-mannitol	70.5 mg
cornstarch	16.0 mg
sodium hydrogencarbonate	15.0 mg
hydroxypropylmethylcellulose	3.0 mg
talc	5.0 mg
magnesium stearate	0.5 mg

Y-128, D-mannitol, cornstarch and sodium hydrogencarbonate were mixed and the mixture was applied to fluidized granulation while spraying an aqueous solution of hydroxypropylmethylcellulose. The granulate was passed through a 24 mesh sieve, and talc and magnesium stearate were added. Using a rotary tablet press (Kikusui Seisakusho Ltd.), tablets weighing 160 mg per tablet were produced. Then, using hydroxypropylmethylcellulose as a film coating base, 6 mg of coating per tablet was applied to give film-coated tablets.

Formulation Example 2: fine granules

Y-128	10 %
D-mannitol	89.5 %
hydroxypropylcellulose	0.5 %

Y-128 and D-mannitol were mixed and an aqueous solution of hydroxypropylcellulose was added. The

mixture was kneaded, granulated and dried at 50°C. The granulate was passed through a 32 mesh sieve to give fine granules.

Formulation Example 3: tablet

Y-128	50.0 mg
D-mannitol	30.0 mg
cornstarch	19.0 mg
sodium hydrogencarbonate	15.0 mg
hydroxypropylmethylcellulose	1.5 mg
talc	4.0 mg
magnesium stearate	0.5 mg

Y-128, D-mannitol, cornstarch and sodium hydrogencarbonate were mixed and the mixture was applied to fluidized granulation while spraying an aqueous solution of hydroxypropylmethylcellulose. The granulate was passed through a 24 mesh sieve, and talc and magnesium stearate were added. Using a rotary tablet press (Kikusui Seisakusho Ltd.), tablets weighing 120 mg per tablet were produced.

Formulation Example 4: fine granules

Y-128	5 %
D-mannitol	92 %
hydroxypropylmethylcellulose	3 %

Y-128 and D-mannitol were mixed and an aqueous solution of hydroxypropylmethylcellulose was added. The mixture was kneaded, granulated and dried at 50°C. The granulate was passed through a 32 mesh sieve to give fine granules.

The pharmacological action of the MAG expression promoter of the present invention is explained in the following by referring to Experimental Examples.

Experimental Example 1

The preparation of nerve cell followed the method of Seung U. Kim (Experimental Protocols for Brain and

Nerve - From cultured cell to functional analysis, ed. Katsuhiko Mikoshiba, Takao Shimizu, Yodosha). That is, an embryo was taken out from a 18-day pregnant female rat (Crj: CD(SD)IGS), from which dorsal spinal nerve root ganglia (hereinafter to be referred to as DRG) was removed under a stereoscopic microscope. DRG was treated with 0.25% trypsin and DNase I at 37°C to disperse the cells. Adherent cells other than nerve cells were removed and the cells (5000 cells) were plated on a polylysine-coated plate. The cells were cultured in DMEM containing 10% FCS supplemented with the nerve growth factor (hereinafter to be referred to as NGF, 50 ng/ml) in a CO_2 incubator. After 3 days of culture, the medium was changed to one containing Ara-C (1 μmol/l) to remove proliferative cells other than the nerve cells.

The preparation of Schwann cells followed the method of Ichiro Matsuoka (Springer Neuroscience Lab Manual 1, ed. Hiroshi Hatanaka, Springer-Verlag Tokyo). That is, the sciatic nerve of a neonatal rat (1 to 3 days postnatal, (Crj: CD(SD)IGS)) was removed under a stereoscopic microscope and adventitia was removed. By treating with trypsin/collagenase and DNase I in CMF-HBSS, the cells were dispersed. Using a culture flask, the cells were cultured in DMEM containing 10% FCS in a CO_2 incubator. After culturing in a medium containing Ara-C, the cells were recovered and the cell suspension was treated successively with anti-Thy 1.1 and rabbit complement to remove cells other than the Schwann cells. Using a collagen-coated culture flask, the cells were cultured in DMEM containing 10% FCS in a CO_2 incubator.

After 1 week from the start of the culture of DRG nerve cells, Schwann cells (20,000 cells) were plated on a plate in which DRG nerve cells had been cultured.

The medium for co-culture was DMEM containing 2 μmol/l of forskolin, 50 ng/ml of NGF and 10% FCS. The next day, after attachment of the Schwann cells, the compound of the present invention (the above-mentioned Y-128, 3 μmol/l) dissolved in dimethyl sulfoxide (DMSO), or, as a positive control compound, ascorbic acid (50 μg/ml) was added every 2 or 3 days. As a negative control compound, the vehicle DMSO was treated in the same manner.

After 2 weeks from the start of the co-culture, myelin was stained according to the method of Eldridge C F et al. (J. Cell Biol., 105, p. 1023-1034 (1987)). That is, the cells were fixed with a 10% neutral buffered formalin solution and preserved at 4°C overnight. After removal of the formalin solution, the cells were fixed again with 0.1% osmium tetroxide solution for 1 h and stained with Sudan Black B stain for 30 min. A stained sample (12 wells for each group) was observed under a microscope, and one view of the part where axon was most noticeably stained in each well was selected and photographed with a Polaroid camera.

Fig. 1 - Fig. 3 show stained axon in each group. In a medium addition group, axon was not stained in any well (see Fig. 1). In an ascorbic acid addition group, axon was stained deep in every well (see Fig. 2). In the compound of the present invention (Y-128) addition group (3 μmol/l), axon was stained as deep as ascorbic acid addition group in 5 wells out of 12 wells (see Fig. 3). From the above-mentioned Experimental Example, it was clarified that the compound of the present invention (Y-128) promoted myelination of axon.

Experimental Example 2

According to the method described in Experimental

Example 1, DRG nerve cells and Schwann cells were co-cultured. A DMSO solution containing the compound of the present invention (Y-128, 1, 3, 10 or 30 μmol/l) or ascorbic acid (50 μg/ml) as a positive control compound was added to the medium every 2 days for 2 weeks. As a negative control compound, the vehicle DMSO was added in the same manner. After 2 weeks from the start of the addition of the compound, the medium was removed and a sample buffer containing sodium dodecyl sulfate (SDS) was added to the well for solubilization of the cells.

A part thereof was separated by polyacrylamide gel electrophoresis and the migrated protein was transferred to a PVDF membrane. By immunoblotting and chemiluminescence, the objective protein was detected on an X ray film. A band detected at about 100 kDa migration was identified as a signal of myelin-related glycoprotein (MAG). The X ray film was scanned and the image was imported to a computer, and the expression of MAG was semi-quantitatively determined using an analysis software, ImageQuaNT (Molecular Dynamics). Fig. 4 shows the MAG expression in the X ray film. From the above-mentioned Experimental Example, it was clarified that the compound of the present invention (Y-128) increased the expression of MAG from the concentration of 3 μmol/l.

Experimental Example 3

According to the method described in Experimental Example 1, DRG nerve cells and Schwann cells were co-cultured. A DMSO solution containing the compound of the present invention (Y-128, 10 μmol/ml) or ascorbic acid (50 μg/ml) as a positive control compound was added to the medium every 2 days. The medium DMSO was added in the same manner as was the negative control compound. In the same manner as in Experimental

Example 2, MAG was quantitatively determined before addition of the compounds and 3, 6, 9, 12, 15 and 18 days after addition. Fig. 5 shows the results.

From the above-mentioned Experimental Example, it was clarified that the compound of the present invention (Y-128) increased the expression of MAG maximally at 6 days and 12 days after the addition, and 18 days later, the expression of MAG disappeared. The time-course changes of MAG expression by the compound of the present invention (Y-128) was the same as that by the positive control compound, ascorbic acid.

Experimental Example 4: Experimental allergic encephalomyelitis (EAE (Experimental Autoimmune Encephalomyelitis))

The myelin basic protein of guinea pig is prepared by extracting the spinal cord homogenate with an acid and allowing precipitation with ammonium sulfate. The myelin basic protein and the same amount of Freund's complete adjuvant (containing 4 mg/ml Mycobacteria H37Ra) are mixed and emulsified. The prepared emulsion (0.1 ml) is injected once to the sole of a hind limb of 8 to 12-week-old female Lewis rat. Y-128 (10 mg/kg) is orally administered once a day for 4 weeks from immediately after EAE induction. After the final administration, the symptom of the rat is scored as follows, based on which the effect is evaluated.

0: no symptom 1: tail hanging down limply
2: paralysis of hind limb 3: paralysis of all limbs 4: on the verge of death 5: death

Experimental Example 5: allergic neuritis (EAN (Experimental Autoimmune Neuritis))

Protein peptide (100 μg, corresponding to 53 - 78 of the amino acid sequence of bovine P2 protein) and the same amount of Freund's complete adjuvant

(containing 0.5 mg/ml Mycobacterium tuberculosis) are mixed and emulsified. The prepared emulsion (0.1 ml) is injected once to the sole of a hind limb of 6 to 8-week-old female Lewis rat. Y-128 (10 mg/kg) is orally administered once a day for 4 weeks from immediately after EAN induction. After the final administration, the symptom of the rat is scored as follows, based on which the effect is evaluated.

0: no symptom 1: tail with weakened force
2: tail hanging down limply 3: disorder in maintaining righting 4: disappearance of righting maintenance 5: ataxic gait
6: mild paralysis of hind limb 7: severe paralysis
8: paralysis of all limbs 9: on the verge of death
10: death

Industrial Applicability

The MAG expression promoter of the present invention is useful as an agent for the prophylaxis and/or treatment of diseases mainly presenting hypomyelination, and further, dysmyelination or demyelination. More particularly, it is useful as an agent for the prophylaxis and/or treatment of diseases of mammals inclusive of human, such as multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration, Charcot-Marie-Tooth disease and the like.

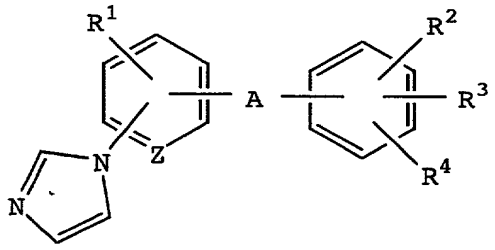
Afterword

This application is based on a patent application No. 144336/1999 filed in Japan, the contents of which are hereby incorporated by reference. The present

invention should not be limited in scope by the specific embodiments described in the specification. Variations and modifications of the present invention will be obvious to those of ordinary skill in the art from the foregoing descriptions. Such variations and modifications are intended to be within the scope of the present invention. Any disclosures by various publications and the like cited herein are hereby incorporated in its entirety into the present invention by reference thereto.

CLAIMS

1. A MAG expression promoter comprising a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof.

2. The MAG expression promoter of claim 1, which is applicable to a disease of mammals inclusive of human, caused by hypomyelination.

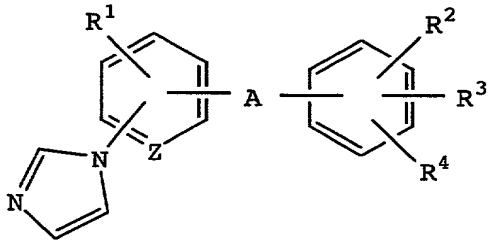
3. The MAG expression promoter of claim 1, which is applicable to a disease of mammals inclusive of human, which disease mainly presents dysmyelination or demyelination.

4. The MAG expression promoter of claim 1, which is applicable to a disease of mammals inclusive of human, which disease being multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration or Charcot-Marie-Tooth disease.

5. The MAG expression promoter of any of claim 1 to claim 4, wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

6. A MAG expression promoter comprising 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof.

7. A method of promoting expression of MAG, which method comprises administering a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is

a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

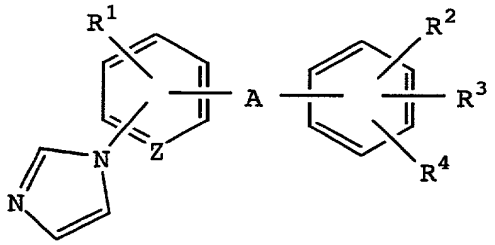
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

8. The method of claim 7, wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

9. A method for promoting expression of MAG, which method comprises administering 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

10. A method for prophylaxis and/or therapy of a disease caused by hypomyelination, which method comprises administering a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is

a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

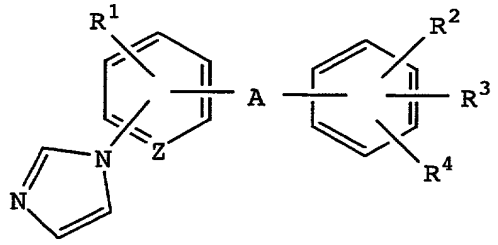
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

11. The method of claim 10, wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

12. A method for prophylaxis and/or therapy of a disease caused by hypomyelination, which method comprises administering 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

13. A method for prophylaxis and/or therapy of a disease mainly presenting dysmyelination or demyelination, which method comprises administering a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

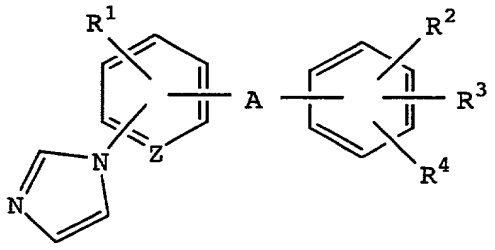
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

14. The method of claim 13, wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

15. A method for prophylaxis and/or therapy of a disease mainly presenting dysmyelination or demyelination, which method comprises administering 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

16. A method for prophylaxis and/or therapy of multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration or Charcot-Marie-Tooth disease, which method comprises administering a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is $-CH(OH)-$, $-C(=O)-$ or $-CH_2-$; and

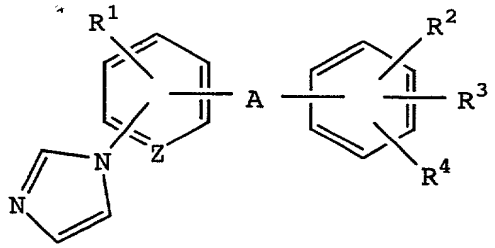
Z is $=CH-$ or $=N-$,

an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

17. The method of claim 16, wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

18. A method for prophylaxis and/or therapy of multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration or Charcot-Marie-Tooth disease, which method comprises administering 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of human.

19. Use of a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, $-COOH$, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is $-CH(OH)-$, $-C(=O)-$ or $-CH_2-$; and

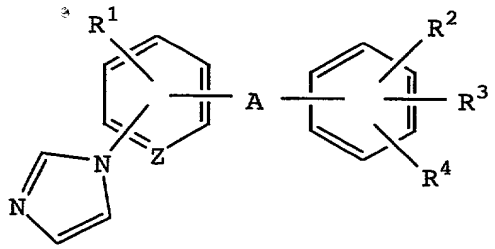
Z is $=CH-$ or $=N-$,

an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter.

20. The use of claim 19, wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

21. Use of 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter.

22. Use of a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, $-COOH$, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is $-CH(OH)-$, $-C(=O)-$ or $-CH_2-$; and

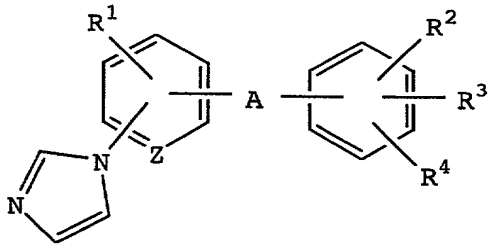
Z is $=CH-$ or $=N-$,

an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of human, which is caused by hypomyelination.

23. The use of claim 22, wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

24. Use of 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of human, which is caused by hypomyelination.

25. Use of a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

Z is =CH- or =N-,

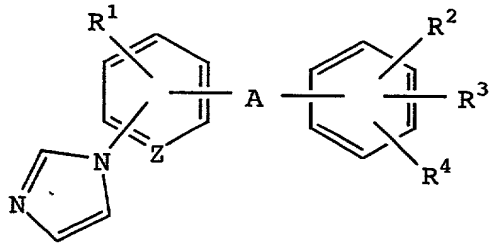
an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of human, which mainly presents dysmyelination or demyelination.

26. The use of claim 25, wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

27. Use of 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of human,

which mainly presents dysmyelination or demyelination.

28. Use of a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

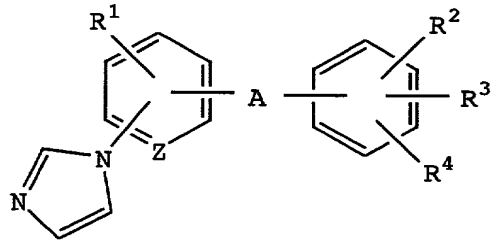
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of human, which is multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration or Charcot-Marie-Tooth disease.

29. The use of claim 28, wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

30. Use of 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of human, which is multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration or Charcot-Marie-Tooth disease.

31. A commercial package comprising a MAG expression promoter comprising a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and R^6 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof and a written matter associated

therewith, the written matter stating that the MAG expression promoter can or should be used for promoting expression of MAG.

32. The commercial package of claim 31, wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

33. A commercial package comprising a MAG expression promoter comprising 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof and a written matter associated therewith, the written matter stating that the MAG expression promoter can or should be used for promoting expression of MAG.

FIG. 1

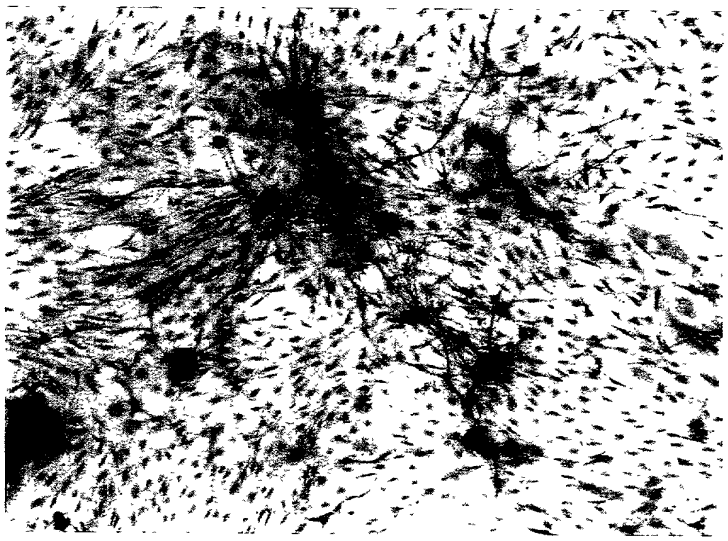


FIG. 2

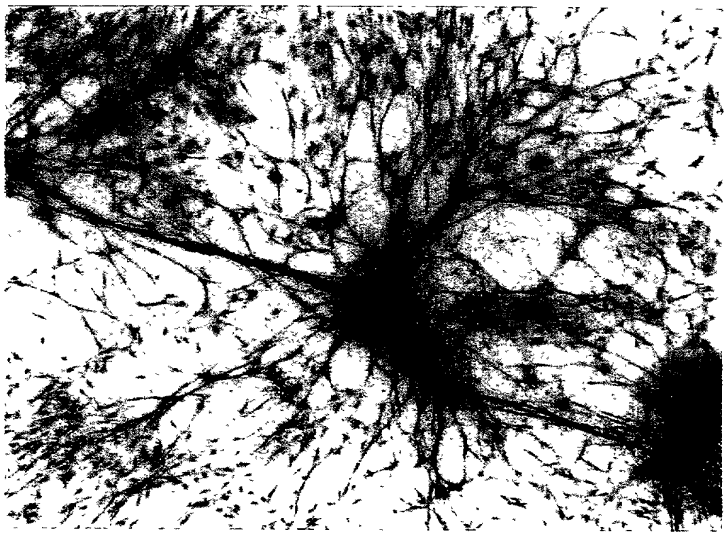


FIG. 3

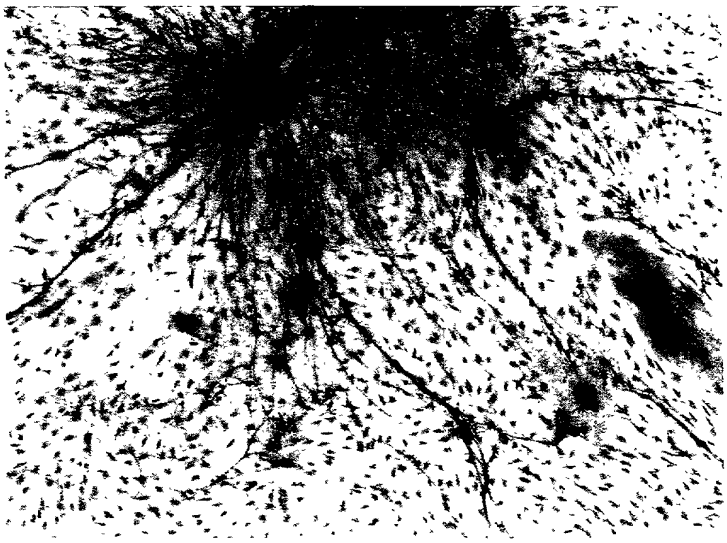
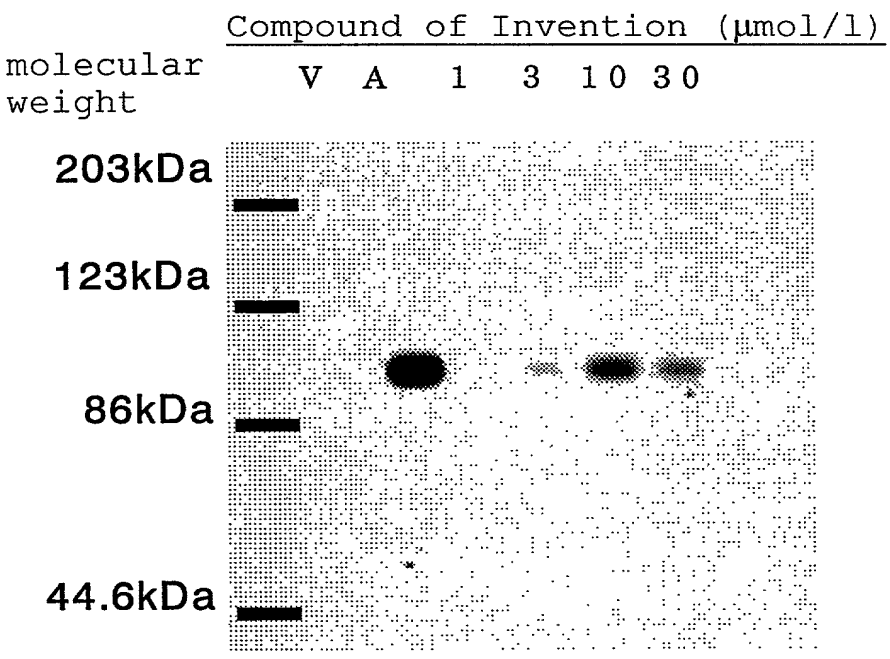


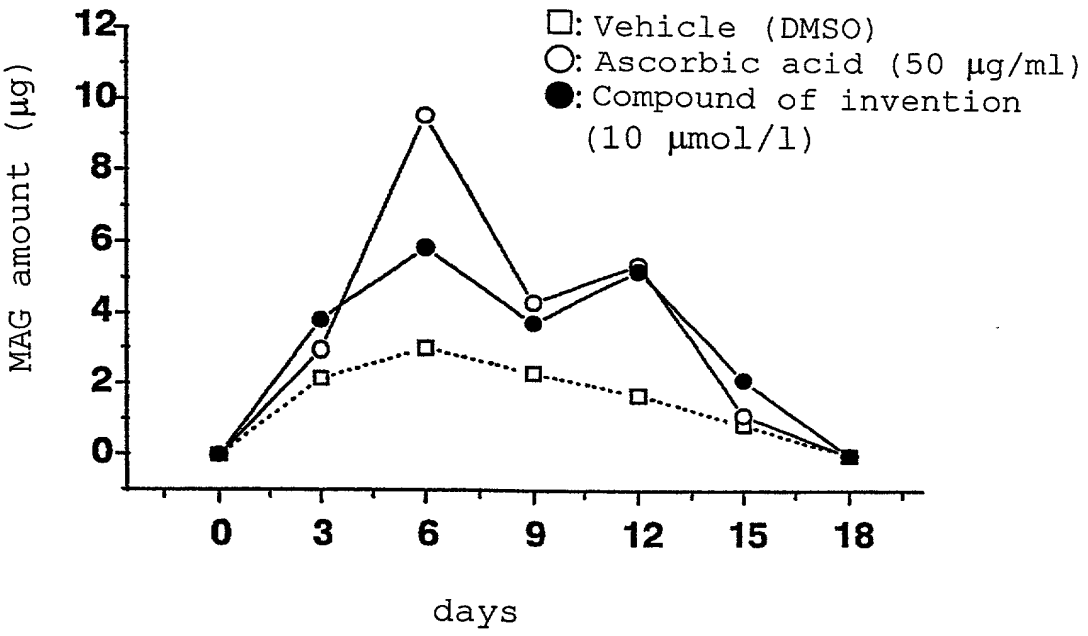
FIG. 4



V: DMSO, A: ascorbic acid (50 μg/ml)

Effect of compound of invention on MAG expression in cultured cell

FIG. 5



Time-course changes in MAG expression after addition of compound of invention

DECLARATION AND POWER OF ATTORNEY FOR U.S. PATENT APPLICATION
米国特許出願宣言書及び委任状

Japanese Language Declaration
日本語宣言書（英語でご記入下さい）

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:
下記の氏名の発明者として、私は以下の通り宣言します。私の住所、郵便物送付先、国籍は下記の私の氏名の後に記載された通りです。下記の名称の発明に関して請求の範囲に記載され、特許出願している発明内容について、私が最初かつ唯一の発明者（下記の氏名が一つの場合）もしくは最初かつ共同発明者（下記の氏名が複数の場合）であると信じています。

Title（発明の名称）： MAG EXPRESSION PROMOTERS

of which is described and claimed in:
上記名称の発明を記述し特許請求する書類は、以下のいずれかです。

( ) the attached specification, or
本状に添付した明細書

(X) the specification in the application Serial No. 09/979,509 filed on November 23, 2001;
提出の米国出願番号 （上記出願番号） で、
and with amendments through _____ (if applicable), or
（該当する場合） （上記日付等） に訂正された明細書

(X) the specification in International Application No. PCT/JP00/03373, filed on May 25, 2000,
and as amended on _____ (if applicable).
（上記日付） 提出の特許協力条約に基づく国際出願番号PCT/ （上記出願番号） で、
（該当する場合） （上記日付等） に訂正された明細書

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.
私は、特許請求の範囲を含む上記訂正後の明細書を検討し、内容を理解していることをここに表明します。

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.
私は、連邦規則法典第37編第1条56項に定義されるとおり、特許性の有無について重要な情報を開示する義務があることを認めます。

I hereby claim priority benefits under Title 35, United States Code, §119 (and §172 if this application is for a Design) of any application(s) for patent or inventor's certificate listed below and have also identified below any application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:
私は、米国法典第35編119条（もし本願が意匠に関する出願の場合は172条）に基き、下記の特許出願又は発明者証の出願についての優先権の利益をここに主張するとともに、優先権主張の基礎となる出願日を有する、本出願の前に出願された特許または発明者証の出願を以下にすべて、枠内をマークすることで示しています。

COUNTRY 国名	APPLICATION NO. 出願番号	DATE OF FILING 出願日	PRIORITY CLAIMED 優先権主張
Japan	144336/1999	May 25, 1999	Yes

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or 365(c) of any PCT international application designating the United States listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which become available between the filing date of the prior application and the national or PCT international filing date of this application:

私は、米国法典第35編120条に基いて下記の米国特許出願、又は米国を指定している特許協力条約365条(c)に基づく優先権をここに主張します。また、本出願の各請求の範囲の技術的事項が米国法典第35編112条第1段で規定された方法で先行する米国特許出願に開示されていない限り、当該先行出願の出願日以降で本出願の国内又はPCTに基づく国際出願の提出日までの期間中に入手できるようになった、連邦規則法典第37編1条56項で定義された特許性の有無に関する重要な情報について、開示義務があることを認識しています。

APPLICATION SERIAL NO. 出願番号	U.S. FILING DATE 米国出願日	STATUS: PATENTED, PENDING, ABANDONED 現状:特許許可済、係属中、放棄済

And I hereby appoint Michael R. Davis, Reg. No. 25,134; Matthew M. Jacob, Reg. No. 25,154; Warren M. Cheek, Jr., Reg. No. 33,367; Nils E. Pedersen, Reg. No. 33,145; Charles R. Watts, Reg. No. 33,142; and Michael S. Huppert, Reg. No. 40,268, who together constitute the firm of WENDEROTH, LIND & PONACK, L.L.P., as well as any other attorneys and agents associated with Customer No. 000513, to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith.
私は、本出願の審査及び本出願に関連するすべてのビジネスに関わる手続きを米国特許商標局に対して遂行するため、共同でWENDEROTH, LIND & PONACK, L.L.P.法律事務所を構成しているMichael R. Davis（登録番号第25,134号）、Matthew M. Jacob（登録番号第25,154号）、Warren M. Cheek, Jr.（登録番号第33,367号）、Nils E. Pedersen（登録番号第33,145号）、Charles R. Watts（登録番号第33,142号）及びMichael S. Huppert（登録番号第40,268号）並びにカスタマー番号第000513号に付帯する他の弁護士及び弁理士を名いたします。

I hereby authorize the U.S. attorneys named herein to accept and follow instructions from TAKASHIMA INTERNATIONAL PATENT OFFICE as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and myself. In the event of a change in the persons from whom instructions may be taken, the U.S. attorneys named herein will be so notified by me.
私は、本願に関して米国特許商標局で行われるあらゆる手続行為に関し、ここに指名した米国弁護士を、弁護士と私との間で直接連絡をとることなく、（米国弁護士が連絡する相手先。譲受人もしくは日本の代理人等）からの指示を受けそれに従うことを、ここに承認します。指示を送る者が変更される場合は、その旨を上記米国弁護士は私から告知されます。

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I further declare that all statements made herein of my own knowledge are true, and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

私は、私自身の知識に基づいて本宣言書中で私が行う表明が真実であり、かつ私の入手した情報と私の信じるところに基づく表明がすべて真実であると信じていること、さらに故意になされた虚偽の表明及びそれと同等の行為は米国法典第18編第1001条に基づき、罰金または拘禁、もしくはその両方により処罰されること、そしてそのような故意による虚偽の声明を行えば、出願した、又は既に許可された特許の有効性が失われることを認識し、よってここに上記のごとく宣誓を致します。

1st Inventor Masakazu Kawasaki Date February 25, 2002
第一発明者（署名、ローマ字もしくは漢字） Masakazu KAWASAKI 署名の日付

2nd Inventor Nobuharu Goto Date January 11, 2002
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3rd Inventor Yoshiharu Hayashi Date January 24, 2002
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4th Inventor Kazuyuki Kawasaki Date January 21, 2002
第四発明者（署名、ローマ字もしくは漢字） Kazuyuki KAWASAKI 署名の日付

The above application may be more particularly identified as follows:
上記出願は、さらに具体的には以下のように特定されます。

U.S. Application Serial No. 09/979,509 Filing Date November 23, 2001
（上記出願日）提出の米国特許出願第（上記出願番号）号

Applicant Reference Number _____ Atty Docket No.
出願人側整理番号（上記番号） 米国弁護士側管理番号（上記番号）

Title of Invention MAG EXPRESSION PROMOTERS
発明の名称